REMARKS/ARGUMENTS

Claims 1, 6-10, 12-15, 18, 19, and 21-29 are active.

Claim 1 is amended to define the concentration of sucrose consistent with previously presented Claims 5, 20 and 21 as well as the specification on page 17, lines 24-26.

Applicants note the Examiner's comment in the Advisory Action that the range of sucrose of 60 to 100 mg/ml may constitute new matter. That opinion is incorrect.

The specification on page 17, lines 24-26 states that sucrose can be present in an amounts ranging from 10 mg/ml to 100 mg/ml or 20 mg/ml to 80 mg/ml or about 60 mg/ml. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon for priority reasonably conveys to the person of skill in the art that the inventor had possession at that time of the later claimed subject matter. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Where specific examples are used to support a claim to a range, the examples must, when taken together with the knowledge of persons skilled in the art, point to the claimed range. *In re Lukach*, 442 F.2d 967, 970 (CCPA 1971). For example, in the case of *In re Wertheim*, 541 F.2d 257 (CCPA 1976), the claims defined a range of 35-50% and were held to be supported by the underlying disclosure having examples at 35% and 50%. Similarly, in the case of *Kolmes v. World Fibers Corp.*, 107 F.3d 1534 (Fed. Cir. 1997), the claims defined a range of 8-12 turns where the underlying disclosure described 4-12 turns, and stated that 8 turns was optimal, and the application at issue claimed 8-12 turns.

Therefore, the disclosure pointed to in the Applicants previous reply and repeated again above on page 17 of the originally filed specification demonstrates possession of the range of sucrose defined in the claims consistent with U.S. law.

Claims 12, 21, 28 and 29 have been amended for clarity and for proper antecedent basis.

No new matter is added.

In addition, as the rejections have already considered the concentrations of sucrose in the pending Action (see page 2 of the Action), no new issues are raised that have not already been considered that would preclude entry of these amended claims notwithstanding the finality of the outstanding Action. In the alternative, should the Examiner maintain the rejections, the presentation of the amended claims is believed to reduce and simplify the issues presented upon appeal as less claims are presented and the subject matter, e.g., in Claim 1, is more specifically defined.

The rejection of Claims 1-2, 4-13, 18-24 and 26-29 under 35 USC 102(e) citing US 2006/0165733 to Betz is respectfully traversed.

Betz mentions sucrose stabilizer only in a long list of possible tonicity adjusting agents in paragraph 42. However, according to this paragraph the preferred tonicity adjusting agent is mannitol. This is also confirmed by Betz's examples which relate to the use of mannitol. Further, citrate buffer is mentioned only as one of several possibilities (see paragraph 40) of "any pharmaceutically acceptable buffer" including, e.g., phosphate buffer, citrate buffer, acetate buffer and formate buffer. Phosphate buffer, not citrate buffer, is preferred according to Betz. Example 2 shows a composition containing a combination of mannitol and phosphate buffer.

Further, Claim 1 is defined to such that the sucrose concentration is 60 mg/ml-100 mg/ml. While Betz discuss that the concentration of the tonicity-adjusting agent is up to *70 mg/ml*, all examples include 30 mg/ml mannitol meaning that Betz's guidance is to a different tonicity agent, other than sucrose, and at a much lower concentration.

The relationship between Betz and that claims is one of a genus and a subgenus. Applicants respectfully submit that the general disclosure in Betz coupled with the specific guidance in the Examples does not qualify as an anticipatory disclosure.

This is not a situation where Betz lists the specific composition (species) and the listing of the specific species is anticipatory (see, e.g., In re Gleave (560 F.3d 1331, USPQ2d 1235 (Fed. Cir. 2009)). When the composition is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various components from a list of alternatives given for placement in specific compositions in a generic disclosure to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). Applicants respectfully submit that one of ordinary skill in the art would not envisage the specific components, in combination, as defined in the claims within the generic teachings and mere listings of possible ingredients provided in the Betz disclosure.

Further, while Applicants understand that a prior art disclosure is not limited to its preferred embodiments but rather all that it teaches, it is also the law that "It is not sufficient that each element be found somewhere in the reference, the elements must be `arranged as in the claim." Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984). See also Ex parte Standish, 10 USPQ2d 1454, 1457 (Bd. Pat. App. & Int'f 1989) ("anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product").

Appellants appreciate and acknowledge the Examiner's discussion that the facts of the present case differ from those of the cited cases, including Lindemann, cited previously. However, it is rare that two cases have similar facts but the holding of the case is still applicable to the present application. That is, simply by Betz listing a plethora of putative

materials that may or may not be included, and indeed, when Betz directs one further to other types of compositions different from those claimed, Betz's generic and meaningless disclosure does not put the composition defined in the present claims in the possession of the public. Betz simply has not arranged the elements of the claims as the law requires.

Thus, Betz does not describe the claimed composition with any specificity to select the classes of tonicity agents, preservatives, etc. such that they "are sufficiently limited or well delineated" to place the claimed composition in the possession of the public. See MPEP §2131.02 and *Ex parte A, Id.*

One may look to the preferred embodiments to determine which compositions can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). The generic disclosure defined in Betz that the Examiner alleges embraces the claimed subject matter embraces potentially thousands of compositions taking into consideration all the optional components and concentration ranges of the buffer, surfactants, tonicity adjusting agents, preservatives, etc.

The breadth of the scope of compositions embraced by Betz is important to the analysis of whether the artisan would envision any one specific, unnamed composition. In *In re Petering*, the prior art disclosed a generic chemical formula that possessed a generic class consisting of about 20 compounds. This decision represents the minimum threshold (one in 20) to hold that a reference "described" the claimed compound or composition such that one of ordinary skill in the art is able to "at once envisage" the compound or composition. As such, when the generic class consists of 20 or less the reference is generally taken to anticipate the claims. However, where the generic class exceeds 20, this should not apply to anticipation rejection.

Accordingly, the Betz disclosure does not anticipate the claims as presented in this paper.

Withdrawal of the rejection is requested.

The Examiner has maintained the obviousness rejection applied under 35 USC 103(a) in view of Betz, Castensson (US 5,567,677) and the McNamara PCT publication (although McNamara is not cited in the introductory section of the rejection). In this rejection, Castensson is cited for the purpose of lower pH in the formulation and the benefit of citrate compared to phosphate buffers. McNamara is cited for the proposition that low pH (of 6.0 or below) enhances the stability of hGH.

Both Betz and Castensson teach that mannitol is the highly preferred tonicity adjusting agent. Castensson fails to disclose sucrose and thus cannot give the skilled person any motivation to use it in liquid formulations of growth hormone. Betz, the only document which makes reference to sucrose, teaches that it is highly preferred to combine phosphate buffer and mannitol to obtain stable liquid formulations of growth hormone. The skilled person would be led away from using sucrose and even more so from combining it with citrate buffer for which there is no experimental basis.

Further, the skilled person had no motivation to use sucrose at a *high concentration of 60mg/ml-100 mg/ml*. This is because Betz shows throughout the examples a lower concentration of its tonicity agent (30 mg/ml mannitol). Castensson teaches in the examples mannitol concentrations of 130 mM to 250 mM, which with a molecular weight of mannitol of 182.17 g/mol translates into concentrations of 23mg/ml -45 mg/ml, thus also below 60-100 mg/ml as currently claimed.

McNamara fails to disclose sucrose and this has been acknowledged by the Examiner. However, it does not clearly teach the use of mannitol as stabilizing agent either and thus the objection that it would be obvious to replace mannitol of McNamara by sucrose is not

correct. McNamara teaches throughout the document that *the stabilizing agents are selected from*

(i) polyethylene-polypropylene glycol non-ionic surfactants such as Pluronics

(ii) taurocholic acid or salts or derivatives thereof, and

(iii) methylcellulose derivatives.

It is only mentioned on page 9 last paragraph that *additional stabilizing excipients* may include, for example amino acids such as glycine or alanine, mannitol or other sugar alcohols or glycerol. Thus, the skilled person is taught by McNamara that it is in principle sufficient to use stabilizing agents chosen from

polyethylene-polypropylene glycol non-ionic surfactants such as Pluronics

taurocholic acid or slats or derivatives thereof, and

methylcellulose derivatives.

Only in exceptional situations one would add one of the additional stabilizing agents reported on page 9. None of these additional excipients is disclosed in the examples of McNamara.

McNamara does not give the incentive to use still another stabilizing agent, namely sucrose, which is nowhere mentioned in McNamara.

The claimed concentration of sucrose from 60 mg/ml to 100 mg/ml corresponds to 6-10% w/v. This is a very high concentration compared to the range of 0.01-5%, preferably 05%-2%, more preferably 0.08-1.0% recommended in McNamara for stabilizing agents (see page 5, lines 15-23 of McNamara). Knowing from McNamara that relatively low concentrations of stabilizing agents selected from the group of polyethylene-polypropylene glycol non-ionic surfactants such as Pluronics, taurocholic acid or salts or derivatives thereof, and methylcellulose derivatives are sufficient, the skilled person would not have had any

incentive to add much higher concentrations of a different stabilizer (sucrose) which is neither disclosed nor suggested in McNamara.

Applicants understand that persons having ordinary skill in the art normally seek "to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). To establish that Applicants' claimed composition would have been obvious to a person having ordinary skill in the art, the prior art must reasonably suggest that persons having ordinary skill in the art do what Applicants claims require. Here, the only suggestion to do what Applicants have done is Applicants' own disclosure, i.e. hindsight.

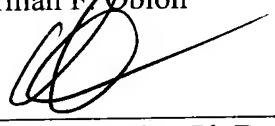
Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. Indeed, this must be true in light of the teachings of the references leading away from the specific combination of ingredients in the claimed formulation.

Reconsideration and withdrawal of the rejection is requested.

A Notice of Allowance is requested for all pending claims.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.
Norman F. Oblon



Daniel J. Pereira, Ph.D.
Attorney of Record
Registration No. 45,518

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/09)

3610706_1.DOC